

	Test	Result
5	Cytotoxicity, Agarose Overlay	Non-cytotoxic
	Cytotoxicity, MEM Elution	Non-cytotoxic
	Intraocular Irritation in the Rabbit with tonometry and specular photography	Non-irritant and non-toxic
10	Mutagenicity, Ames Soluble Chemical Sensitization (Maximization Method), in Guinea Pig Hemolysis, <i>In vitro</i> Direct Contact	Non-mutagenic
	Systemic Antigenicity in Guinea Pig Primary Skin Irritation Rabbit	Non-irritant
	Acute Oral Toxicity Acute Intraperitoneal Toxicity in Mouse	Non-toxic Non-toxic
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It was concluded from these studies that the HPMC solution is non-toxic, non-mutagenic, non-antigenic, non-hemolytic, non-irritating, non-inflammatory to ocular tissues, and did not cause a dangerous intraocular pressure rise. Further, the material had no effect on the ability of the cells to undergo normal mitotic division and, subsequently, normal cellular growth. Intraocular pressure increases in the rabbit from a maximum dose were transient and, in all cases, were within the normal range within a 24 hour period. Endothelial cells were not affected.

Although the present invention has been described in considerable detail with reference to a certain preferred versions and uses thereof, other versions and uses are possible. For example, while the viscoelastic solution is designed for ophthalmic applications, it may be used for other physiological applications such as lubricating bone joints (knees, hips, etc.), preventing tissue adhesion following surgical procedures, or as a carrier for nutritional products or cosmetics. Also, the viscosity of the solutions can be varied by selecting different molecular weight starting materials or blending the materials in different proportions or using higher concentrations of the starting materials. While a particular blend of HPMC materials is disclosed the combination selected and concentrations can depend on the desired properties of the end product. Therefore, various different HPMC may be used. Further, it is not necessary that two different materials be used. One HPMC material may be processed as described above or a blend of more than two materials may be used. Additionally, different salts and buffers can be used for different applications and other materials can be added to the solutions for special purposes. Further, one skilled in the art will recognize that a different combination of filters may be used to remove debris and, depending on the dimensions and nature of debris in the composition, one or more of each size of filter can be used. Also, the order in which various processing steps are performed may be interchanged. Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred versions contained herein.

What is claimed is:

- 65 1. An improved composition for physiological applications, said composition containing hydroxypropylmethylcellulose in a physiological salt solution, the improvement comprising a hydroxypropylmethylcel-

harmful

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~~1. A solution free of particulate matter and gels [greater than 0.5 μm in diameter], said viscoelastic solution having a zero shear viscosity in excess of 15,000 cps, an average molecular weight in excess of 250,000 Daltons and being pyrogen free and non-toxic when a therapeutic amount of said solution is injected into a human body.~~

~~2. The improved composition of claim 1 wherein said composition being pyrogen free and non-toxic when a therapeutic amount of the solution is injected into a human eye.~~

~~3. The viscoelastic solution of claim 2 wherein the hydroxypropylmethylcellulose is present in a concentration from about 2.0% to about 2.5%.~~

~~4. The viscoelastic solution of claim 2 wherein the viscosity of the solution is from about 25,000 centipoise to about 40,000 centipoise.~~

~~5. The viscoelastic solution of claim 2 wherein the average molecular weight of the hydroxypropylmethylcellulose is greater than about 375,000 but less than 420,000.~~

~~6. The viscoelastic solution of claim 2 prepared from a blend of a first hydroxypropylmethylcellulose having a first molecular weight and a second hydroxypropylmethylcellulose having a greater molecular weight, the blend being processed to produce the particulate free, pyrogen free, and non-toxic solution.~~

~~7. The viscoelastic solution of claim 6 wherein the blend is processed by filtration, redissolving and removal of low molecular weight material, mid-process autoclaving and removal of dissolved gases.~~

~~8. The viscoelastic solution of claim 7 wherein the hydroxypropylmethylcellulose in the viscoelastic solution after processing has an average molecular weight greater than the average molecular weight of the first hydroxypropylmethylcellulose or the second hydroxypropylmethylcellulose.~~

~~9. The viscoelastic solution of claim 6 wherein the first hydroxypropylmethylcellulose has an average molecular weight of about 85,000 and the second hydroxypropylmethylcellulose has an average molecular weight of about 220,000.~~

~~10. The viscoelastic solution of claim 8 wherein the average molecular weight of the hydroxypropylmethylcellulose after processing is greater than 375,000 but less than 420,000.~~

~~11. The viscoelastic solution of claim 6 having a hydroxypropylmethylcellulose concentration of about 2.3%.~~

~~12. The viscoelastic solution of claim 5 wherein the hydroxypropylmethylcellulose has an average molecular weight of about 410,000.~~

~~13. A process for preparing a viscoelastic solution of hydroxypropylmethylcellulose in a physiological salt solution, the composition being free of particulate matter and gels [greater than 0.5 μm in diameter] and being pyrogen free and non-toxic when a therapeutically effective amount of said solution is injected into a human eye, the process comprising the steps of:~~

~~a) dispersing the hydroxypropylmethylcellulose in the salt solution to form a suspension.~~

~~b) heating the suspension of step (a) to about 95° C., allowing any undissolved material to settle and discarding the supernatant liquid above the undissolved material.~~

~~c) resuspending the undissolved material to form a second suspension of hydroxypropylmethylcel-~~

harmful

- lucose and heating the second suspension to form a thick gel.
- 5       d) filtering the gel through a series of filters [the series including a final filter having 0.5 $\mu$ m openings] to form a clear solution,
- e) autoclaving the clear solution,
- f) cooling the autoclaved clear solution and filtering the cooled solution, and
- g) degassing the filtered cooled solution.
- 10      14. The process of claim 13 wherein the physiological salt solution has a pH of about 8.7 and contains NaCl, KCl, CaCl<sub>2</sub>·2H<sub>2</sub>O, MgCl<sub>2</sub>·6H<sub>2</sub>O, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>·3H<sub>2</sub>O, NaC<sub>6</sub>H<sub>5</sub>O<sub>7</sub>·2H<sub>2</sub>O.
- 15      15. The process of claim 13 wherein the hydroxypropylmethylcellulose dispersed in the aqueous salt solution is a blend of a first hydroxypropylmethylcellulose having a first molecular weight and a second hydroxypropylmethylcellulose having a higher molecular weight.
- 20      16. The process of claim 15 wherein the first hydroxypropylmethylcellulose has a molecular weight of about 85,000 Daltons and the second hydroxypropylmethylcellulose has a molecular weight of about 220,000 Daltons.
- 25      17. The process of claim 15 wherein the weight of the first hydroxypropylmethylcellulose in the suspension is about the weight of the second hydroxypropylmethylcellulose.
- 30      18. The process of claim 15 wherein the hydroxypropylmethylcellulose in the suspension is about 3% by weight.
- 35      19. The process of claim 13 wherein the concentration of the hydroxypropylmethylcellulose in the degassed solution is from about 2.0% to about 2.5%.
- 40      20. The process of claim 13 wherein the concentration of the hydroxypropylmethylcellulose in the degassed solution is about 2.3%.
- 45      21. The process of claim 13 wherein the viscosity of the degassed solution is from about 25,000 centipoise to about 40,000 centipoise.
- 50      22. The process of claim 13 wherein the viscosity of the degassed solution is about 40,000 centipoise.
- 55      23. The process of claim 13 wherein the molecular weight of the hydroxypropylmethylcellulose in the degassed solution is greater than about 375,000 but less than about 420,000.
- 60      24. The process of claim 11 wherein the molecular weight of the hydroxypropylmethylcellulose in the degassed solution is about 410,000.
- 65      25. A viscoelastic composition for injection into a human eye, the viscoelastic composition comprising hydroxypropylmethylcellulose in a physiological salt solution,
- 70      the hydroxypropylmethylcellulose having an average molecular weight greater than about 375,000 but less than about 420,000 and being present in a concentration from about 2.0% to about 2.5%.
- 75      the composition having a viscosity from about 25,000 centipoise to about 40,000 centipoise, being free of harmful
- 80      particulate matter and gels [greater than 0.5  $\mu$ m in diameter] and being pyrogen free and nontoxic.
- 85      26. The viscoelastic composition of claim 25 wherein the concentration of the hydroxypropylmethylcellulose is about 2.3%, the average molecular weight of the hydroxypropylmethylcellulose is about 409,800 and the zero shear viscosity of the composition is about 40,000 centipoise.

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27. A process for preparing a high viscosity, sterile solution of hydroxypropylmethylcellulose in an aqueous solution, the high viscosity, sterile solution being non-toxic, non-pyrogenic, and substantially free of particulate matter and gels harmful to the human eye, the process comprising the steps of:

- 5      a) dispersing hydroxypropylmethylcellulose in a first part of the aqueous solution to form a suspension;
- 10     b) allowing the suspension to settle to yield a supernatant and a sediment comprising high molecular weight hydroxypropylmethylcellulose;
- 16     c) discarding the supernatant, and leaving the sediment;
- 20     d) resuspending the sediment in a second part of the aqueous solution to form a gel;
- 25     e) filtering the gel through a series of successively finer filters to remove harmful particulate and gelatinous matter to form a clean solution; and
- 30     f) sterilizing the clean solution.

*plurality*

28. The process of step 27, wherein step a) is performed at a sufficiently elevated temperature to solvate low molecular weight hydroxypropylmethylcellulose, and step e) is performed at a sufficiently elevated temperature to significantly reduce the viscosity of the gel.

29. The process of claim 28, wherein the sterilization of the clean solution is effected by autoclaving.

30. The process of claim 29, comprising the further steps of:

- a) cooling the autoclaved clean solution;
- b) filtering the cooled solution; and
- c) degassing the filtered, cooled solution.

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